Presenters
Dr. Jane Lewis
Dr. Mary Ellen Counts
Dr. Richard Solana
Dr. Roger Walk

PM3000185933

Harm Reduction of Cigarettes

- There is no safe cigarette.
- We agree that smoking causes lung cancer and other diseases.
- PM USA takes the pursuit of harm reduction as a priority and does so in a responsible manner.
- PM USA shares the public health community's concern about smoker's exposure to smoke that can cause and augment disease.
- We welcome the input of the CDC on issues discussed today as well as those referenced in our letter dated July 22, 2004.

PM3000185934

Our Approach to Harm Reduction of Cigarettes

Includes:

- Reduction of tobacco specific nitrosamines (TSNA) in leaf tobacco
- Electrically heated cigarette smoking system (EHCSS)
- Smoke Constituent Reduction program (SCoR)

PM3000185935

TSNA and PAH in Harm Reduction

- The public health community has identified some TSNAs* as possible[1] and some PAHs** as probable[2] causes of disease in smokers, but their relative contribution is unknown.

- If possible, PM USA will reduce TSNAs in tobacco used in our products, but their reduction is not sufficient for a reduced exposure/risk/harm claim.

PM3000185936

* Tobacco specific nitrosamines
** Polycyclic aromatic hydrocarbons

1-IARC Monographs, Suppl. 7, 68, 1987
2-IARC Monographs, Suppl. 7, 58, 1987

TSNA and PAH in Harm Reduction

"The [TSNA] NNK is an organ-specific carcinogen that induces adenocarcinoma in the peripheral lung of mice, rats, and hamsters." *Dietrich Hoffmann, Institute for Cancer Prevention American Health Foundation (2001)*

By use of a weight-of-evidence approach, specific PAHs and [TSNA] NNK can be identified as probable causes of lung cancer in smokers, but the contribution of other agents cannot be excluded."
Stephen S. Hecht, PH.D., University of Minnesota Cancer Center (1999)

PM3000185937

Outline

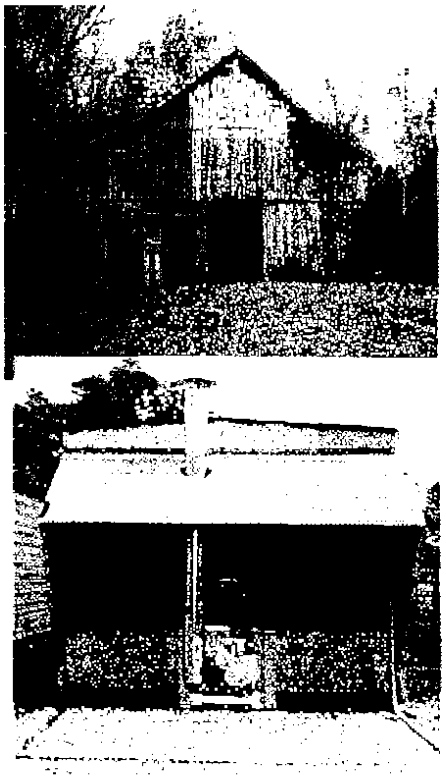
- TSNAs in tobacco
- TSNAs and PAHs in cigarette smoke
- Reduction of TSNAs, PAHs and other smoke constituents in the gas/vapor phase and/or particulate phase (SCoR program and Electrically Heated Cigarette Smoking System)
- Comprehensive process to assess exposure reduction
- Exposure measurement
  - Smoking topography
  - Biomarkers
- Summary

PM3000185938

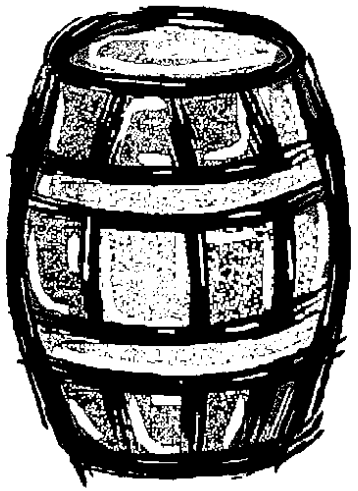
Tobacco Processing

Burley

Air-curing barn



STEMMERY



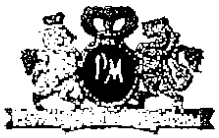
Storage

Bright

Flue-curing barn with heat exchanger

PM300018593 9

TSNA Levels and Their Reduction: Domestic Flue-Cured Tobacco



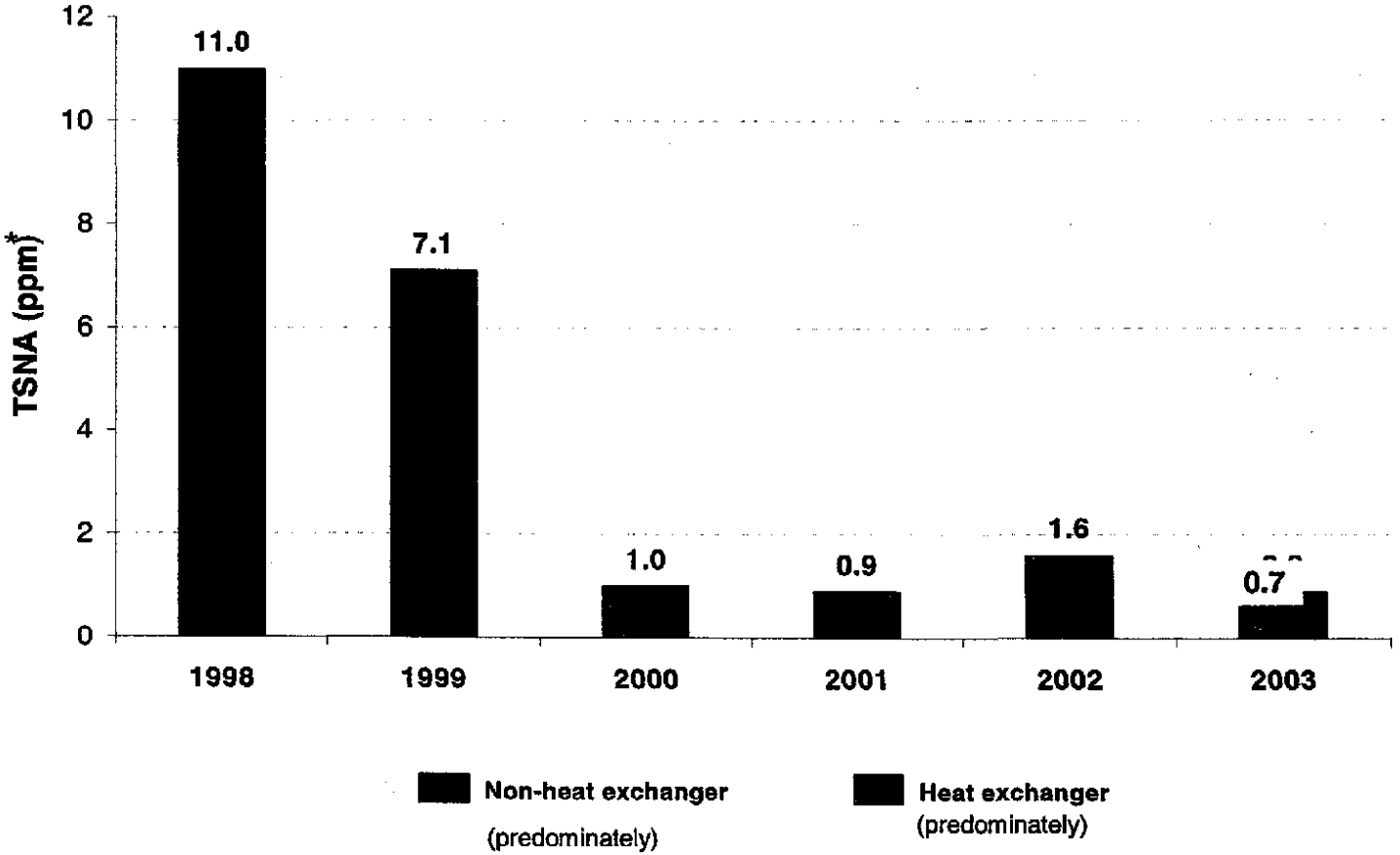
- Recognition in the late 1990s by R.J. Reynolds Tobacco Company that the use of direct-fired propane heaters increases TSNAs in flue-cured tobacco. *
- Heat exchangers decrease TSNA levels by approx. 80-90%.
- In Feb. 2000, PM USA contributed $35 million to the *Flue-Cured Tobacco Cooperative Stabilization Corporation* which aided farmers with $66 million to install heat exchangers. **
- Since 2001, PM USA *Tobacco Farmer Partnering Program* requires the use of heat exchangers.

PM3000185940

* *Peele, D.M; et al., "Formation of tobacco-specific nitrosamines in flue-cured tobacco", Recent Adv. Tob. Sci. 27: 3-12; 2001*

** *"Philip Morris USA Has Worked With American Farmers to Significantly Reduce the Level of Nitrosamines In American Grown Tobacco" PM USA press release, May 30, 2003*

TSNA Levels and Their Reduction: Domestic Flue-Cured Tobacco



1998-1999 measurement taken at the end of curing by RJR* *

2000 - measurement taken at the end of curing by PM USA

1998 - 2000 measurements were of a limited number of barns and are not necessarily representative of the entire crop year

2001 - 2003 measurement taken at receiving stations by PM USA

N for 2001 – 2003 is 175 to 259

* NNN, NAT, NAB, NNK

** Peele, D.M; et al., "Formation of tobacco-specific nitrosamines in flue-cured tobacco", Recent Adv. Tob. Sci. 27: 3-12; 2001

PM300185941

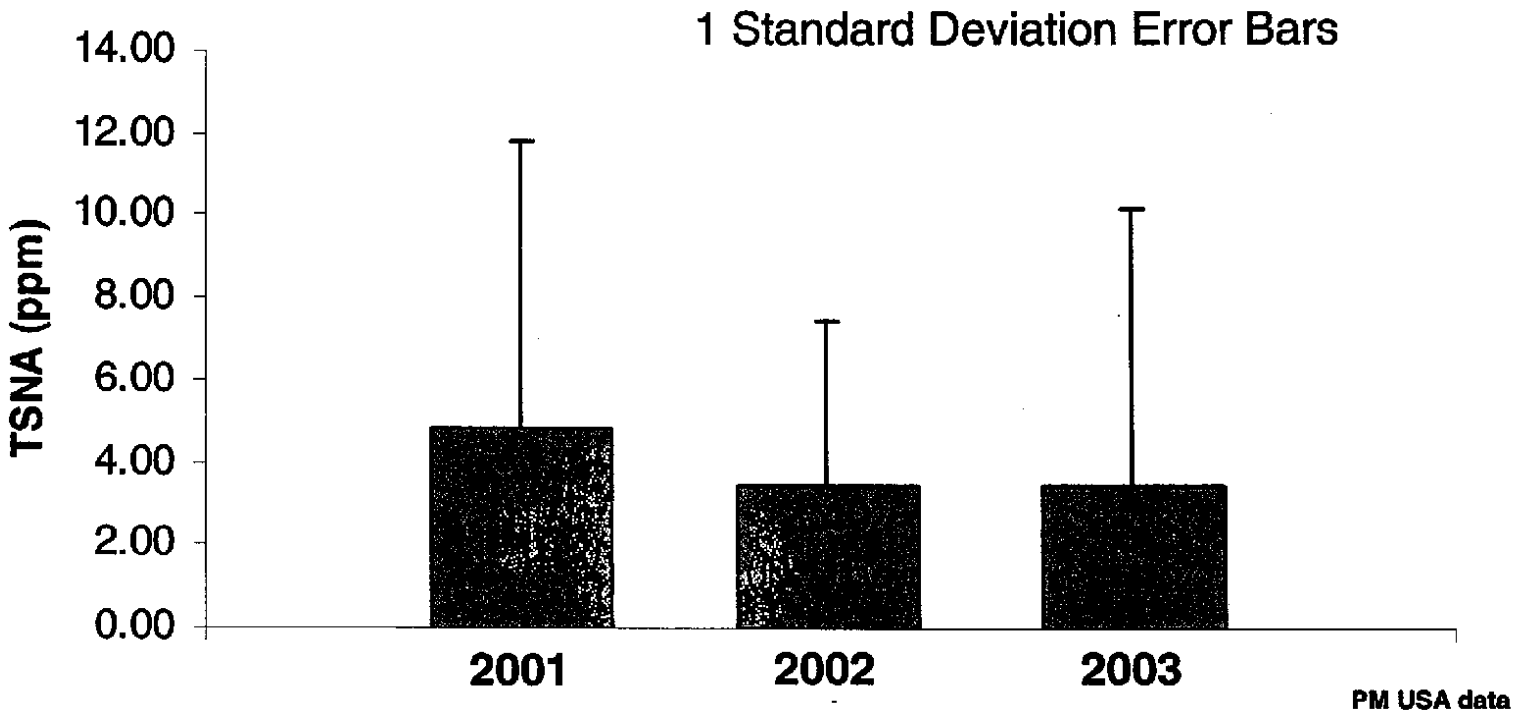
TSNA Levels and Their Reduction: Domestic Air-Cured Tobacco

- No single approach is effective for reducing TSNAs in air-cured tobacco.

- Strategies to reduce TSNA levels
  - Seed screening ("cleaning")
  - Ongoing internal and external research
    - Reducing fertilizer usage
    - Modifying storage and handling practices
    - Increasing barn ventilation
    - Raising endogenous antioxidants

PM3000185942

Domestic Air-Cured Tobacco:
Monitoring of TSNAs* at Time of Purchase



PM3000185943

2001 - 2003 measurements taken at receiving stations.

Is not representative of air-cured tobacco used in PM blends

* NNN, NAT, NAB, NNK

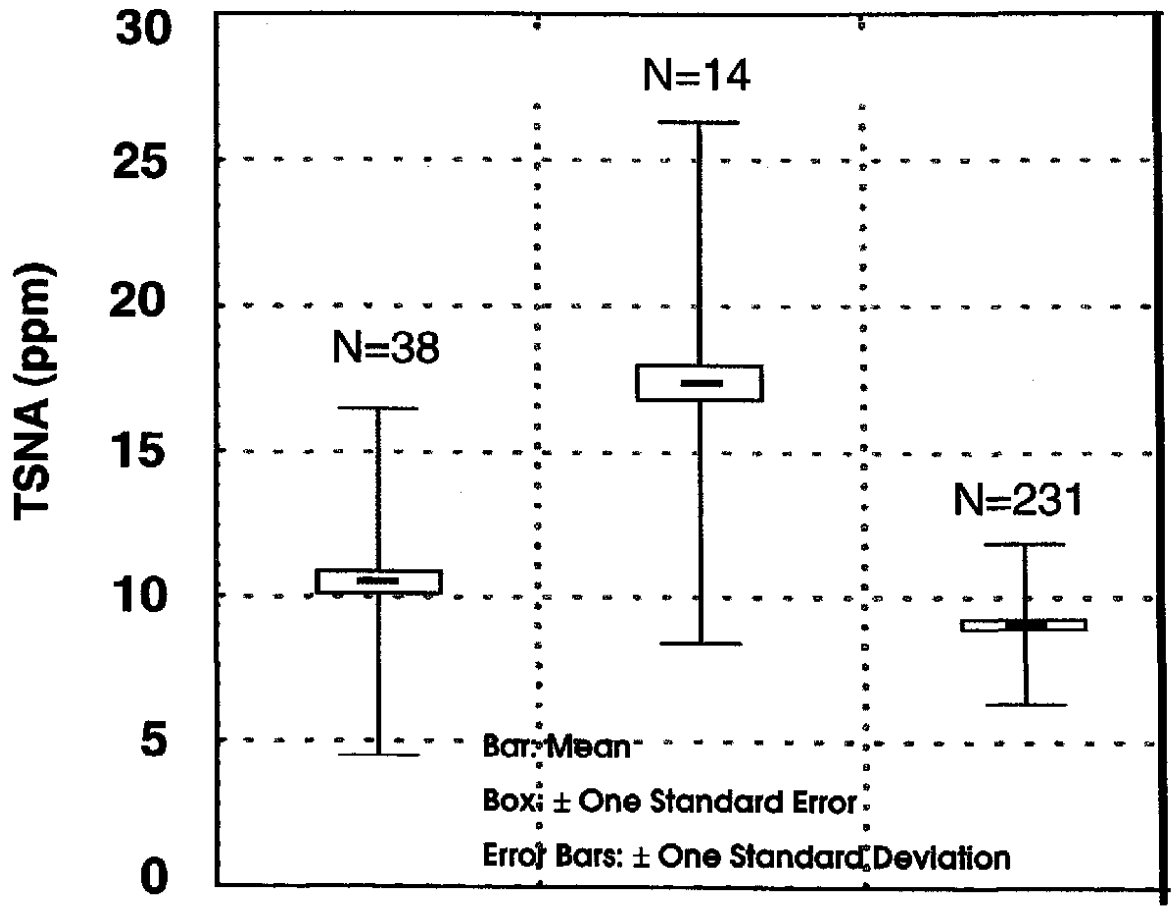
TSNA Levels and Their Reduction: Reconstituted Leaf

- Reconstituted leaf (RL) is the product of a paper making-like process that uses a "feedstock" of tobacco stems, pieces of tobacco lamina and other materials primarily from air-cured and flue-cured tobacco.

- Measures implemented in 2000 to reduce TSNA formation during this process:
  - Additional microbial growth control
  - Additional process standards (e.g., temperature)
  - Refined cleaning schedules for each process stage
  - Fresh instead of recycled process water in the extraction-redilution stage

PM3000185944

Monitoring of TSNAs in Reconstituted Leaf*



* NNN, NAT, NAB, NNK

Data acquired 2000-2001

PM USA

PM3000185945

Summary: TSNAs in Tobacco

- Supported by our research efforts, we are making progress in reducing levels of TSNAs in the domestic tobacco we purchase for our cigarette products.

- We are monitoring the effect of TSNA reduction in tobacco on the levels in cigarette smoke.

PM3000185946

TSNAs and PAHs in Mainstream Smoke

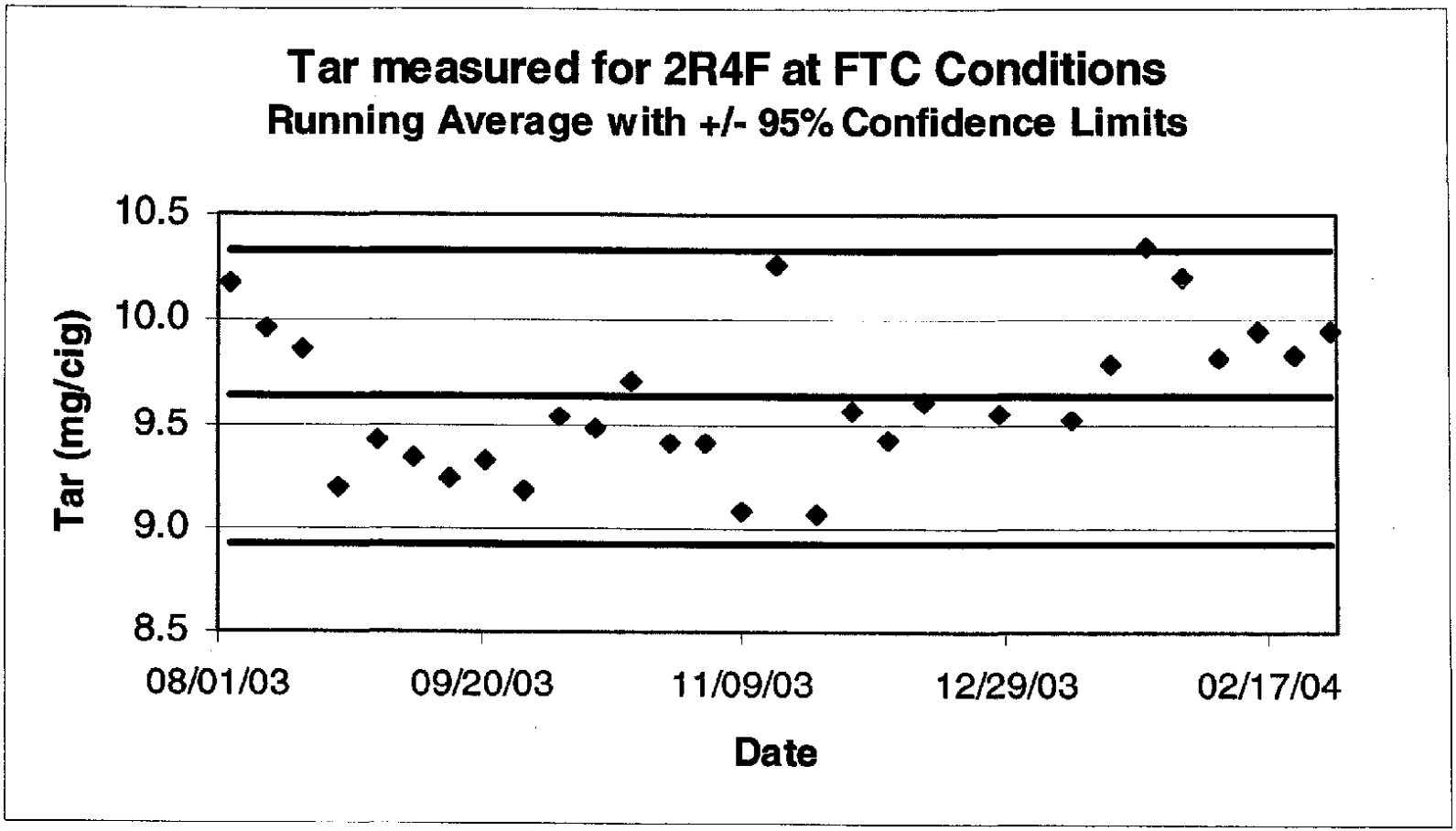
- *Massachusetts Benchmark Study-1999*
  - 26 (10 PM USA) commercial brand styles
  - Massachusetts Department of Public Health (MDPH) machine smoking conditions: 45cc, 30 s, 50% filter ventilation blockage
- *Market Mapping Studies – 2002 and 2004*
  - 26 (11 PM USA) commercial brand styles - 2002
  - 5 (5 PM USA) commercial brand styles – 2004
  - Federal Trade Commission (FTC) machine smoking conditions (35 cc, 60 s, no vent blocking)
- *Electrically Heated Cigarette Smoking System (EHCSS) – Accord brand style*

PM3000185947

Variability in Smoke Constituent Analysis

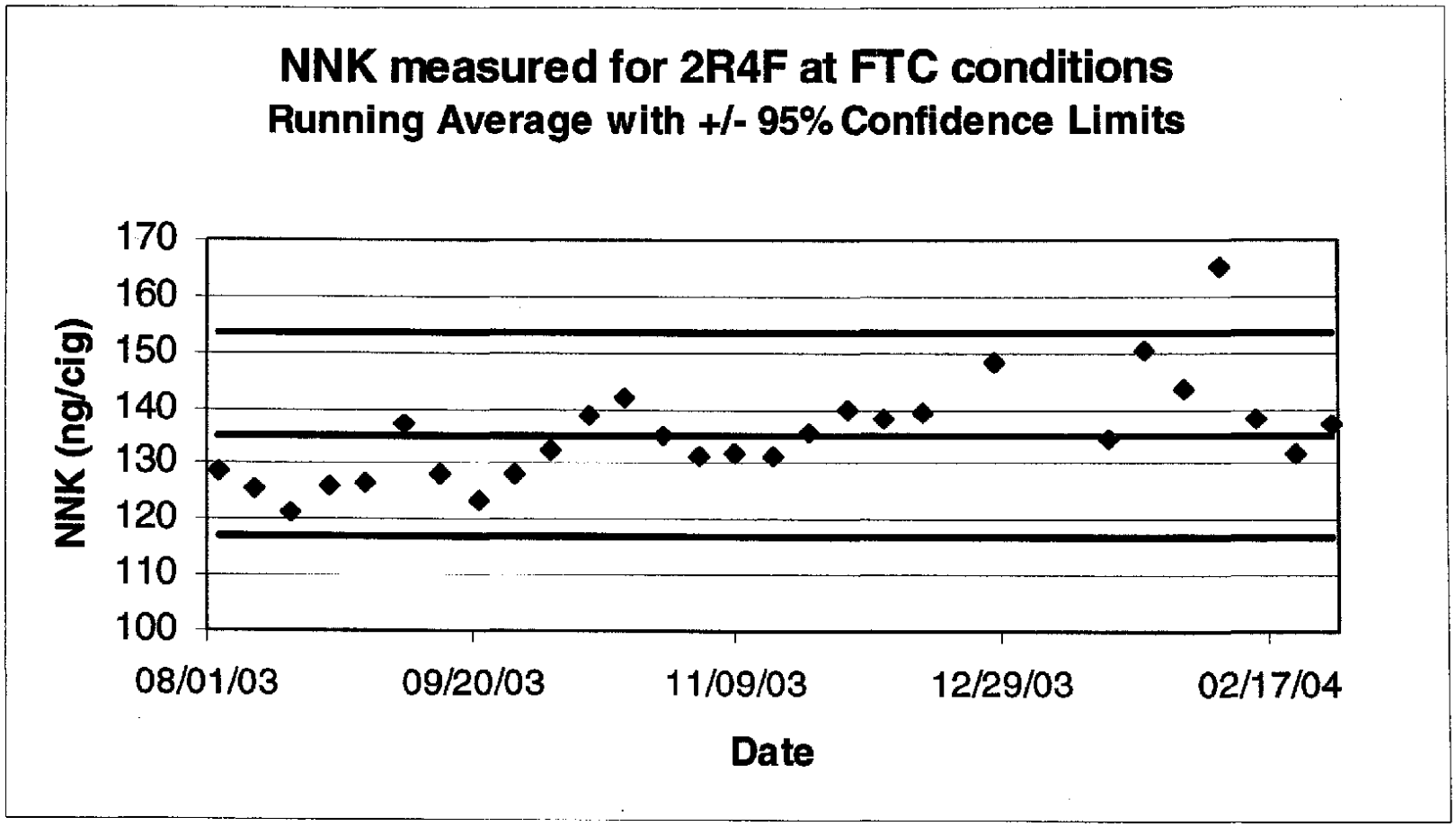
- Within-Laboratory: acceptable day-to-day variability for validated methods
- Between-Laboratory: currently no standardized and inter-laboratory validated smoke analysis methods except for FTC and ISO tar, nicotine, and carbon monoxide
- Comparing smoke constituent data from different sources is a challenge without standardized methods.
- Standardized methods will be needed in regulated environments having cigarette performance standards and/or reporting requirements.

PM3000185948



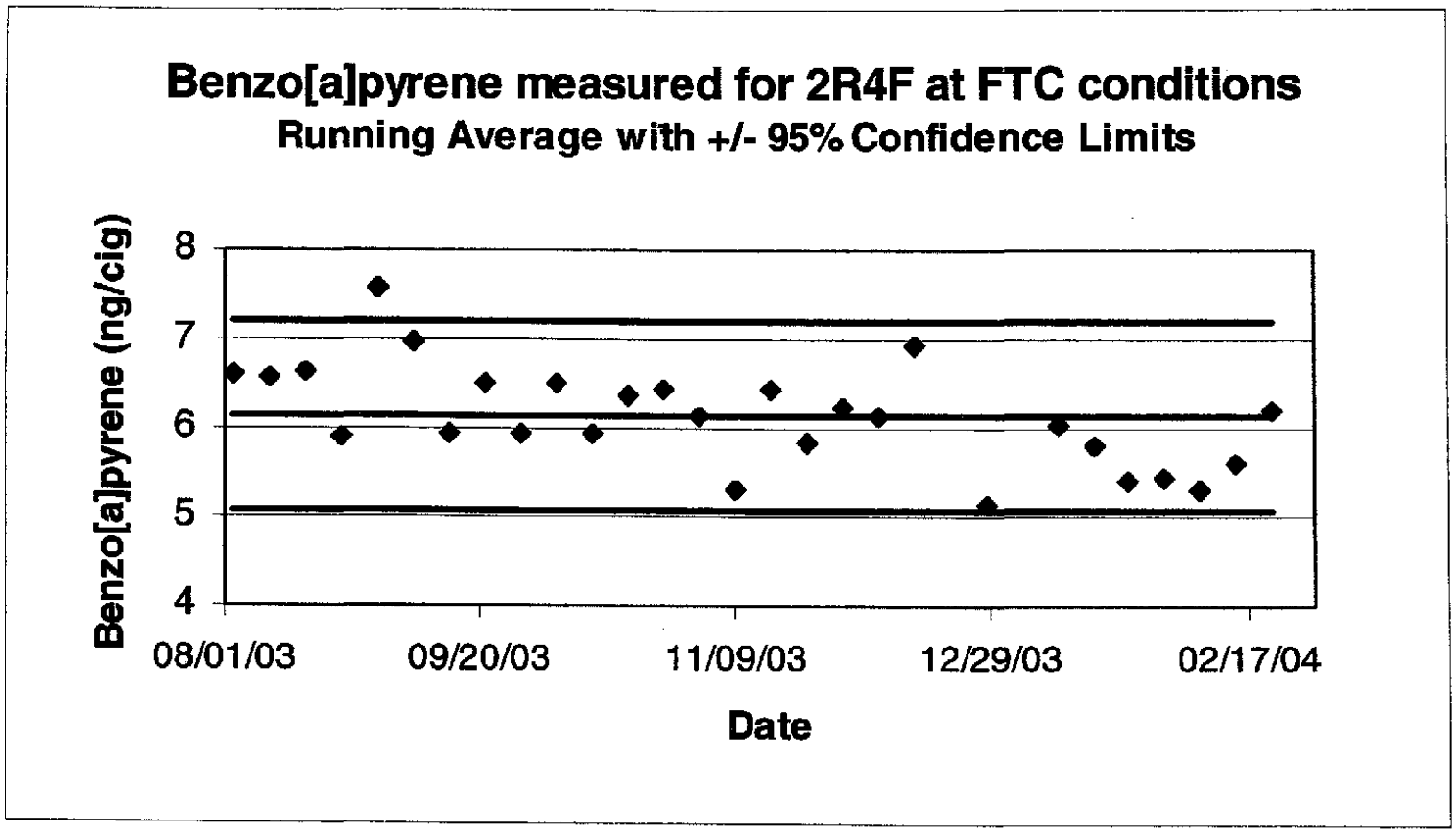
Source: PM USA Laboratory (ISO 17025 accredited)

PM3000185949



Source: PM USA Laboratory (ISO 17025 accredited)

PM3000185950

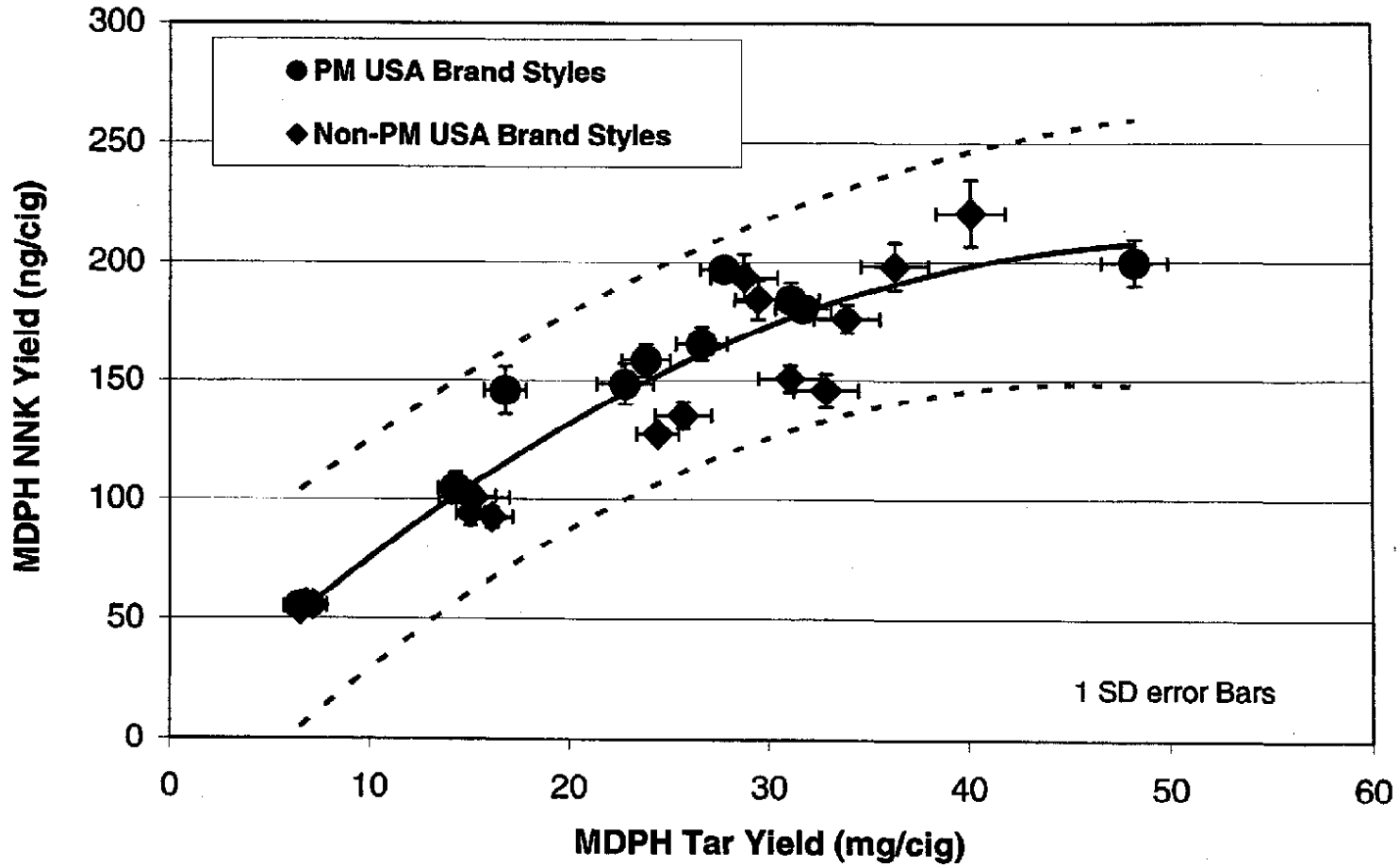


Source: PM USA Laboratory (ISO 17025 accredited)

PM3000185951

1999 Massachusetts Dept. of Public Health (MDPH) Benchmark Study

MDPH *NNK** yields and MDPH Tar Yields

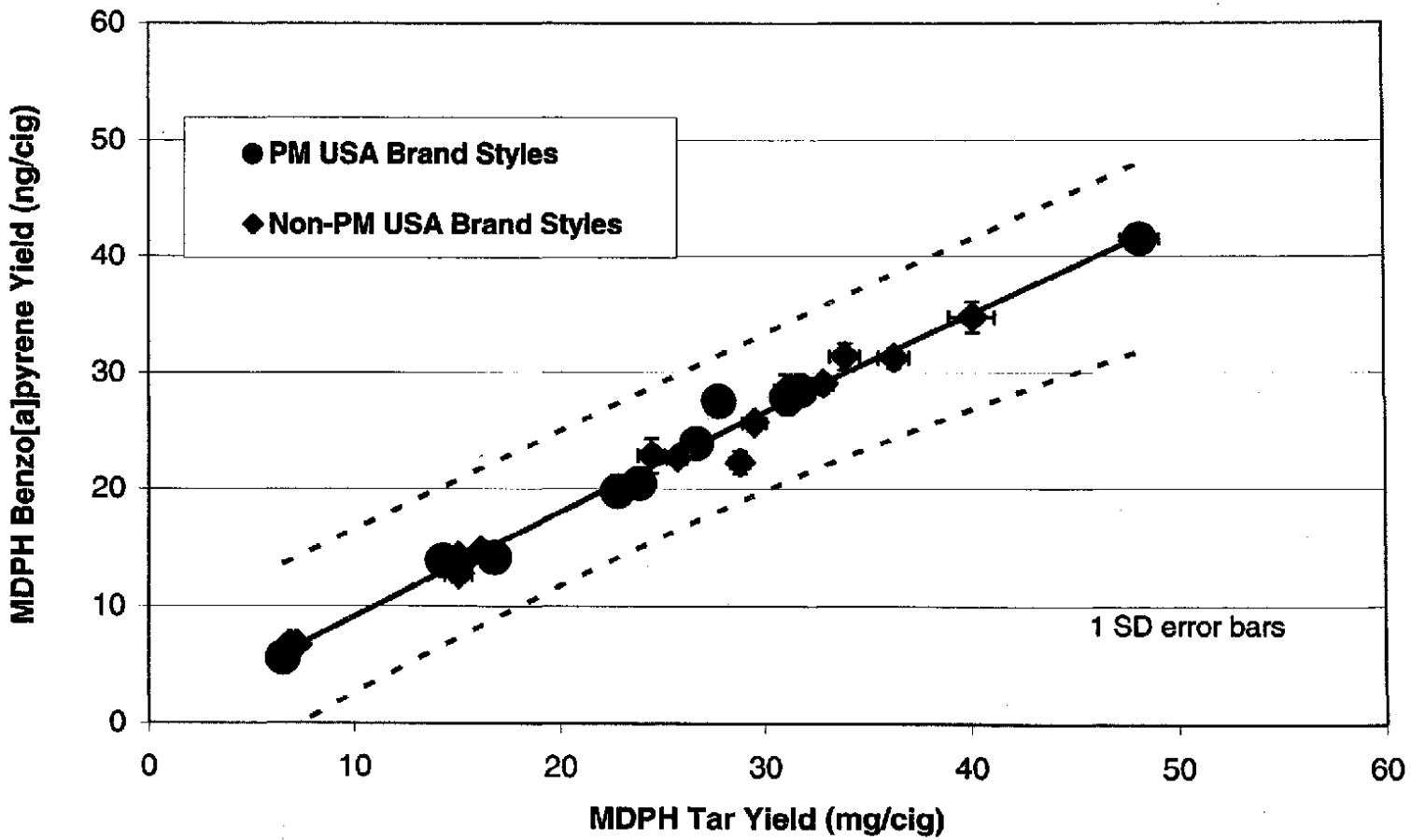


*4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone

PM3000185952

1999 Massachusetts Dept. of Public Health (MDPH) Benchmark Study

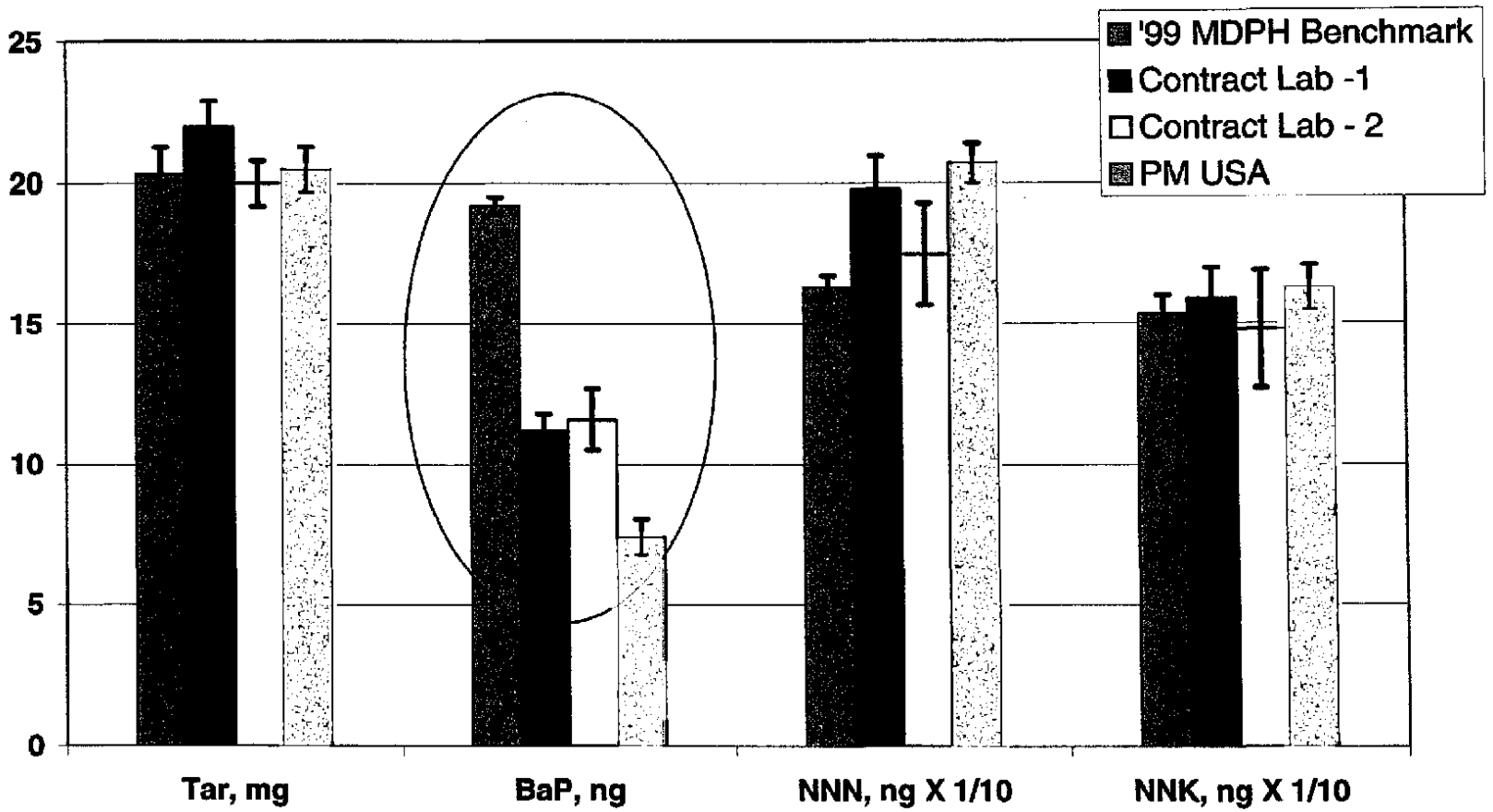
MDPH *Benzo[a]pyrene* Yields with MDPH Tar Yields



PM3000185953

1R4F Reference Cigarette Yields at MDPH Machine Conditions

Points-in-Time Between-Lab Variability Examples

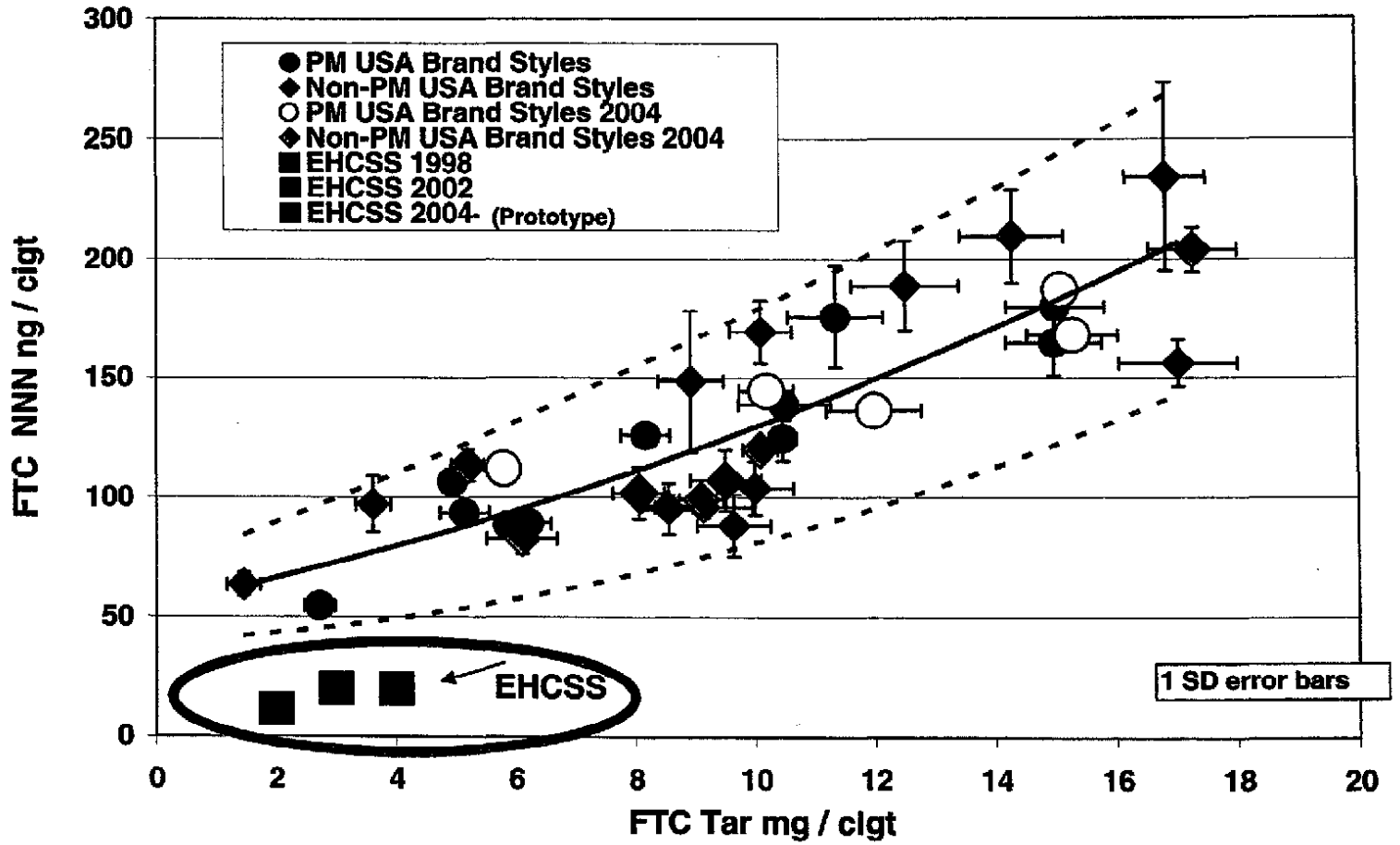


1 SD Error Bars

PM3000185954

2002 and 2004 Domestic Brand FTC Mapping

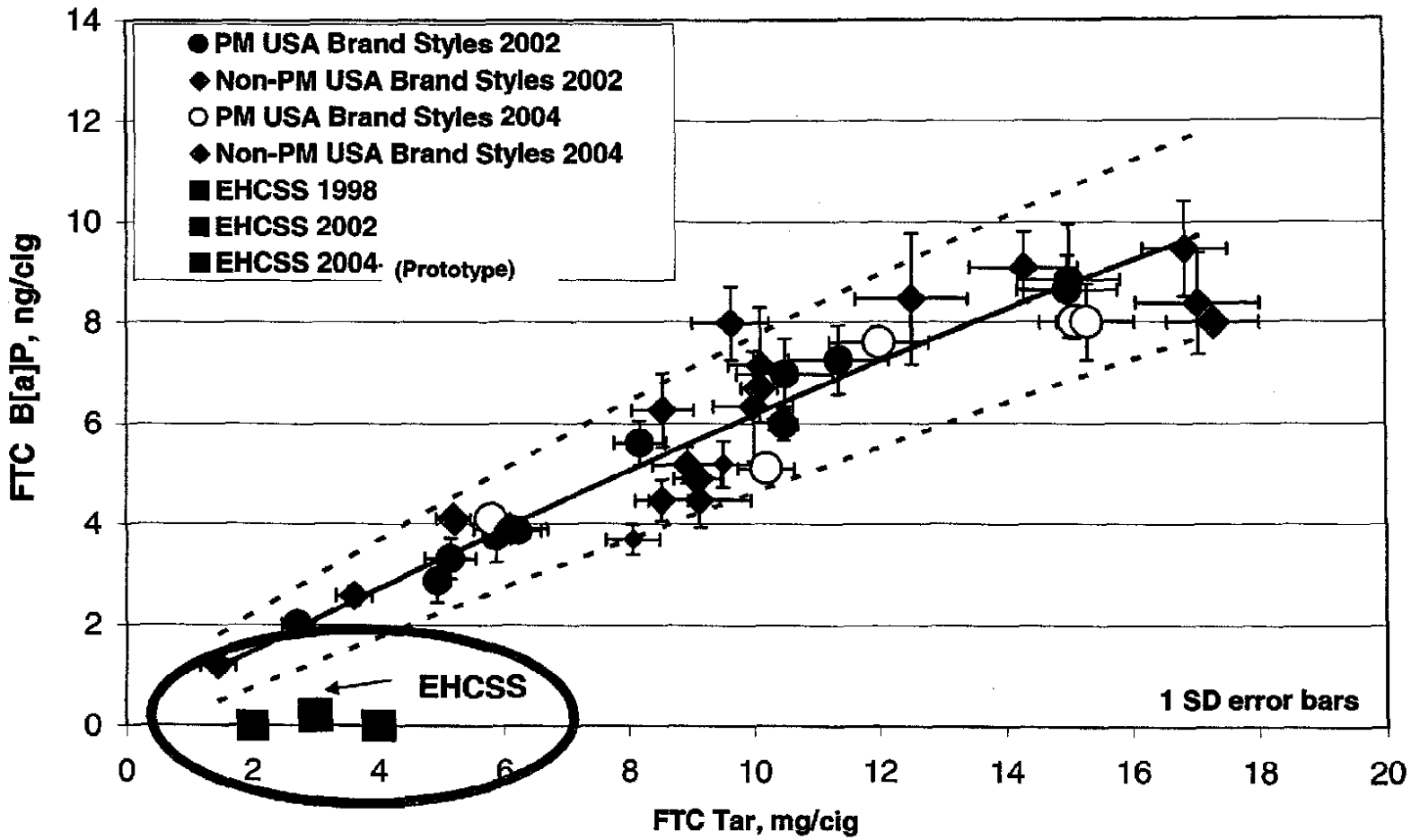
FTC *NNN** Yield with FTC Tar Yield



*N-Nitrosonornicotine

PM3000185955

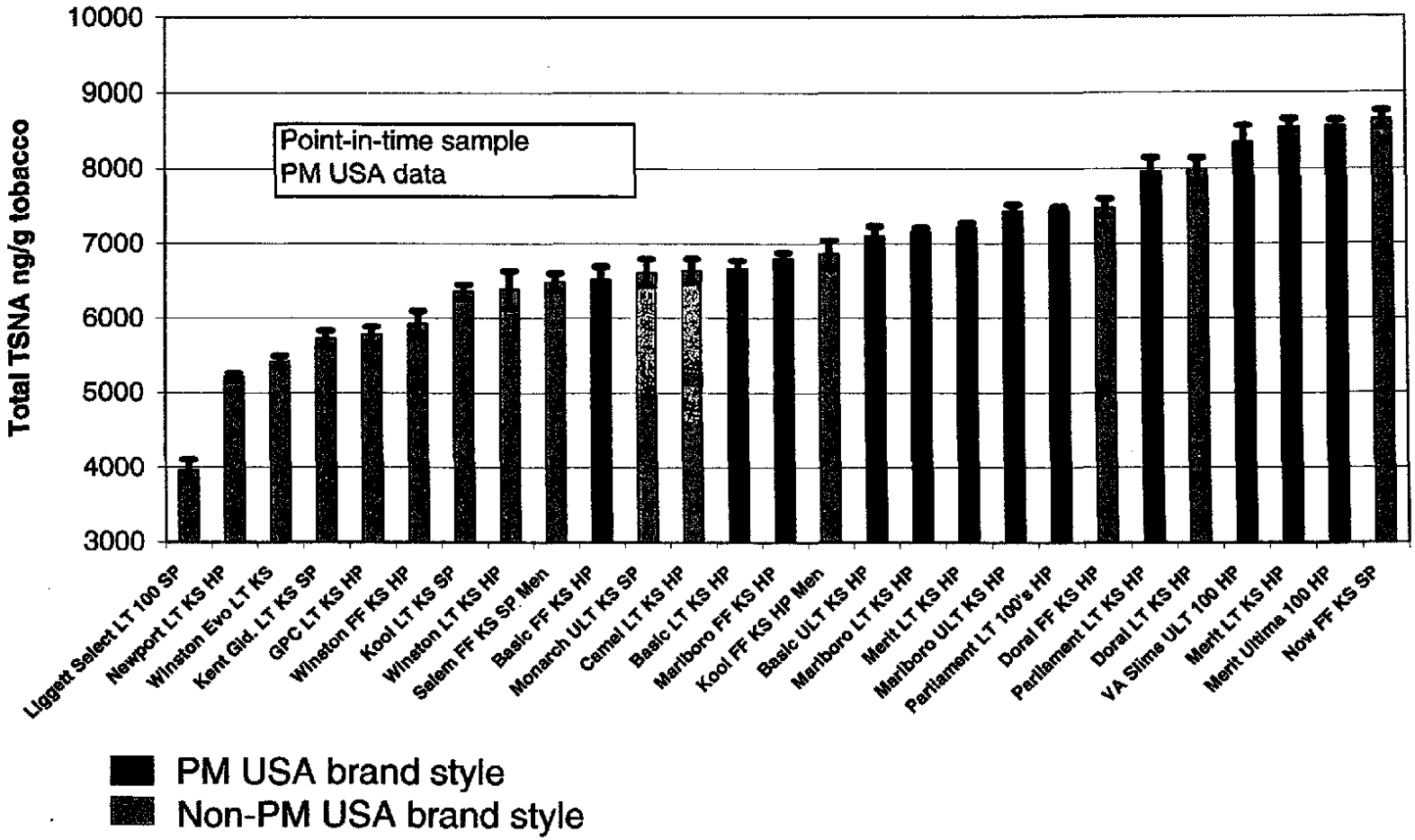
2002 and 2004 Domestic Brand FTC Mapping
FTC *Benzo[a]pyrene* Yield with FTC Tar



PM3000185956

2002 Domestic Market Brand Styles

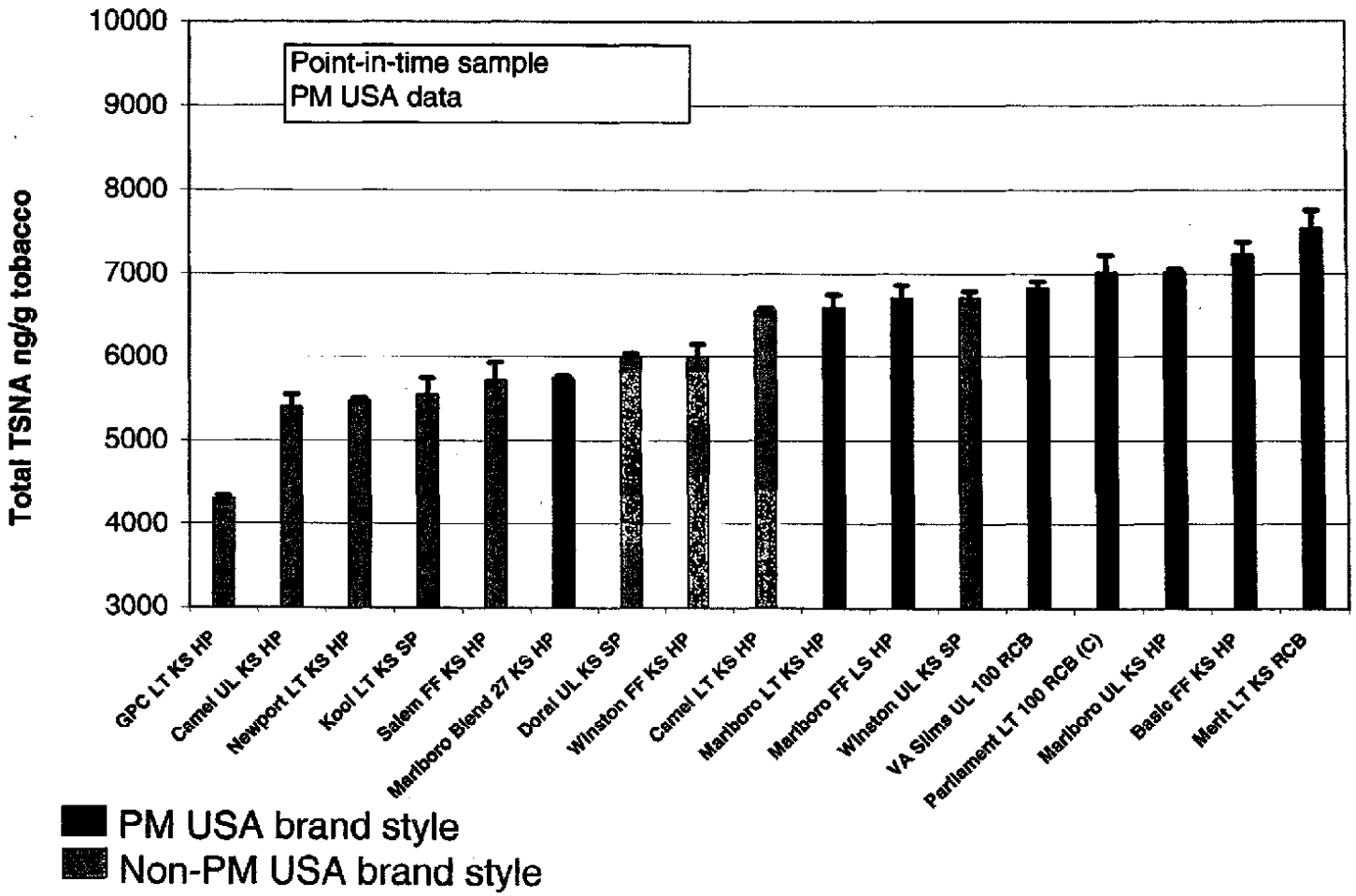
Total Tobacco TSNA ng/g = NNN + NNK + NAT + NAB



PM3000185957

2004 Domestic Market Samples

Total Tobacco TSNA ng/g = NNN + NNK + NAT + NAB



PM3000185958

Variability over Time

- **Short-term** (days)
  - Variability in tobacco weight, filter ventilation, blend uniformity, etc., around targets
- **Medium-term** (months)
  - Components (papers, filters, ventilation), tobacco blend grades and sources
- **Long-term** (years)
  - Tobacco crop year inventories, component suppliers, cigarette design changes

PM3000185959

ISO Standard 8243, Appendix C

Summary: TSNAs and PAHs in Cigarette Smoke

- Smoke constituent yields are a function of product design and tobacco blends used in those designs.
- TSNA and PAH yields generally correlate with tar in current commercial lit-end cigarettes.
- We have reduced both TSNAs and PAHs in cigarette smoke by heating rather than burning tobacco.
- Within-lab and between-lab analytical variability and product variability over time should be considered when assessing smoke constituent yield data.

TSNAs, PAHs and Other Mainstream Smoke Constituents

Selection Criteria:

1. *CPSC (1993)*
2. *Known smoke constituents: IARC (1986)*
3. *Classified as carcinogens: IARC (1998)*

Parameters
- total particulate matter
- water
- nicotine
- tar
- carbon monoxide

Aliphatic Hydrocarbons
- 1,3-butadiene
- Isoprene

Aldehydes
- Acetaldehyde
- Acrolein
- Formaldehyde
- Propionaldehyde

Polycyclic Aromatic Hydrocarbons
- benz(a)anthracene
- benzo(b)fluoranthene
- benzo(j)fluoranthene
- benzo(k)fluoranthene
- benzo(a)pyrene
- dibenz(a,h)anthracene
- dibenz(a,e)pyrene
- dibenz(a,h)pyrene
- dibenz(a,i)pyrene
- dibenz(a,l)pyrene
- indeno(1,2,3-cd)pyrene
- 5-methylchrysene

Phenols
- catechol
- phenol

Aromatic Amines
- 4-aminobiphenyl
- o-anisidine
- 2-naphthylamine
- o-toluidine

N-Nitrosamines
- nitrosodibutylamine
- nitrosodiethanolamine
- nitrosodiethylamine
- nitrosodimethylamine
- nitrosodipropylamine
- nitrosomethylethylamine
- nitrosonomicotine
- nitrosopiperidine
- nitrosopyrrolidine
- NNK

Monocyclic Aromatic Hydrocarbons
- benzene
- styrene
- toluene

Polycyclic Aza-arenes
- dibenz(a,h)acridine
- dibenz(a,j)acridine

Aliphatic Nitrogen Compounds
- acetamide
- acrylonitrile
- 1,1-dimethylhydrazine
- hydrogen cyanide
- 2-nitropropane
- urethane

Halogen Compounds
- vinyl chloride

Metals
- arsenic
- cadmium
- chromium
- nickel
- lead

Inorganic Compounds
- hydrazine
- nitrogen oxides

PM3000185961

Examples of Technologies Used in Our Smoke Constituent Reduction Program (SCoR)

- Carbon filter technology (highly activated)
  - 70-90% reduction in some gas/vapor phase smoke constituents (under FTC conditions)
  - No selective reduction in particulate phase smoke constituents at this time

- Lower TSNA flue-cured and air-cured tobacco used in the blend

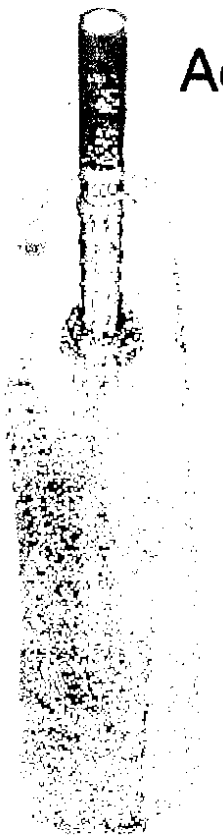
PM3000185962

Electrically Heated Cigarette Smoking System (EHCSS) *(ACCORD)**

Conventional Cigarette

- Tobacco Temp: 900° C
- Uncontrolled Heating

Accord

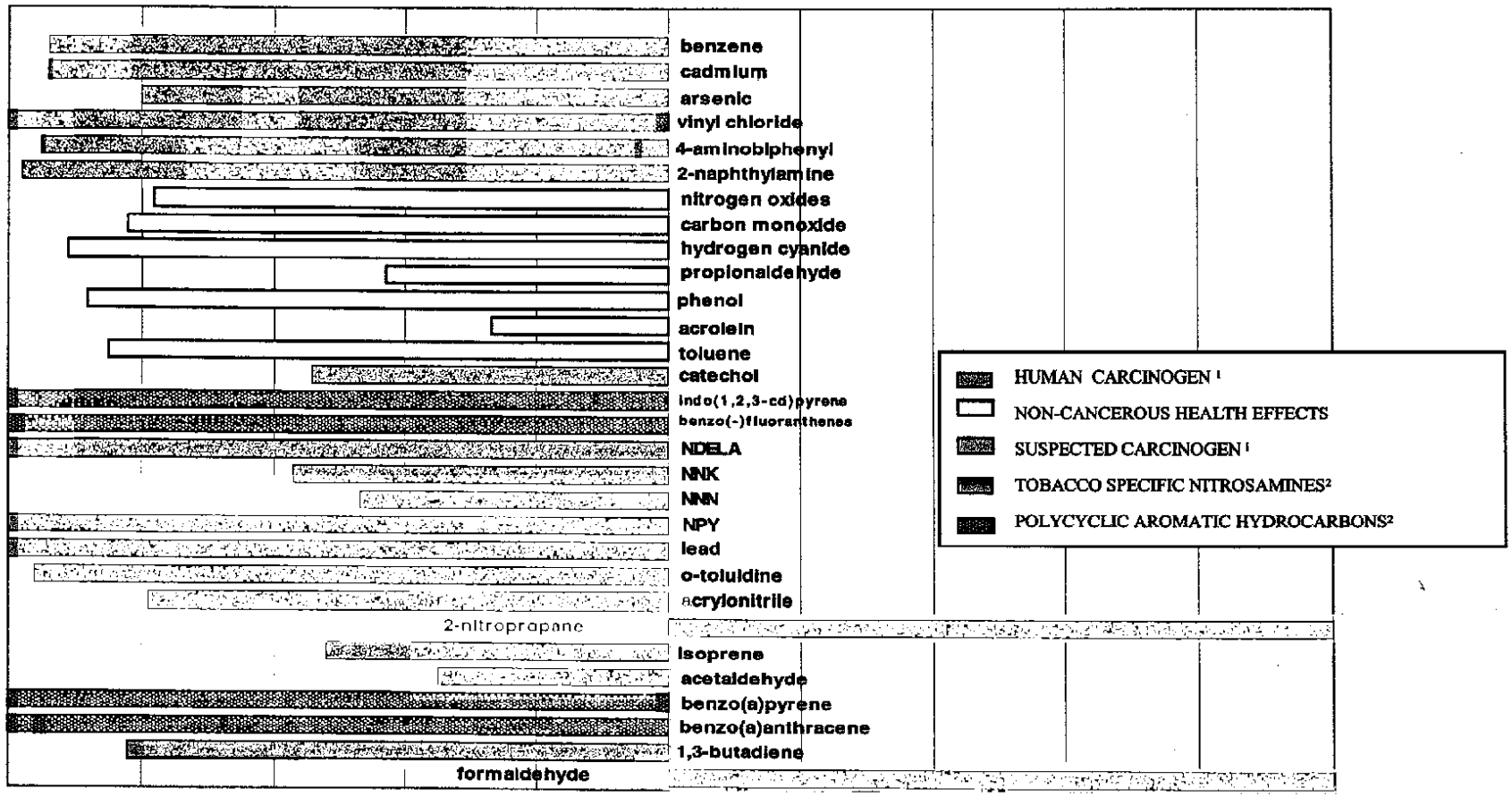


- Tobacco Temp: <500° C
- Controlled Heating

PM3000185963

Electrically Heated Cigarette Smoking System: Smoke Constituents

Amounts compared to a standard reference cigarette (1R4F) (per mg of TPM)



PM3000185964

Electrically Heated Cigarette Smoking System: Smoke Constituents

- *TSNAs and PAHs as well as many other mainstream smoke constituents of both the gas/vapor phase and the particulate phase are dramatically reduced compared to a standard reference cigarette.*

- *A few smoke constituents are increased vs. same standard reference cigarette (EHCSS, 1st generation).*

- *Reduced exposure substantiation requires a battery of chemical/biological/clinical tests to provide data for a weight of evidence assessment.*

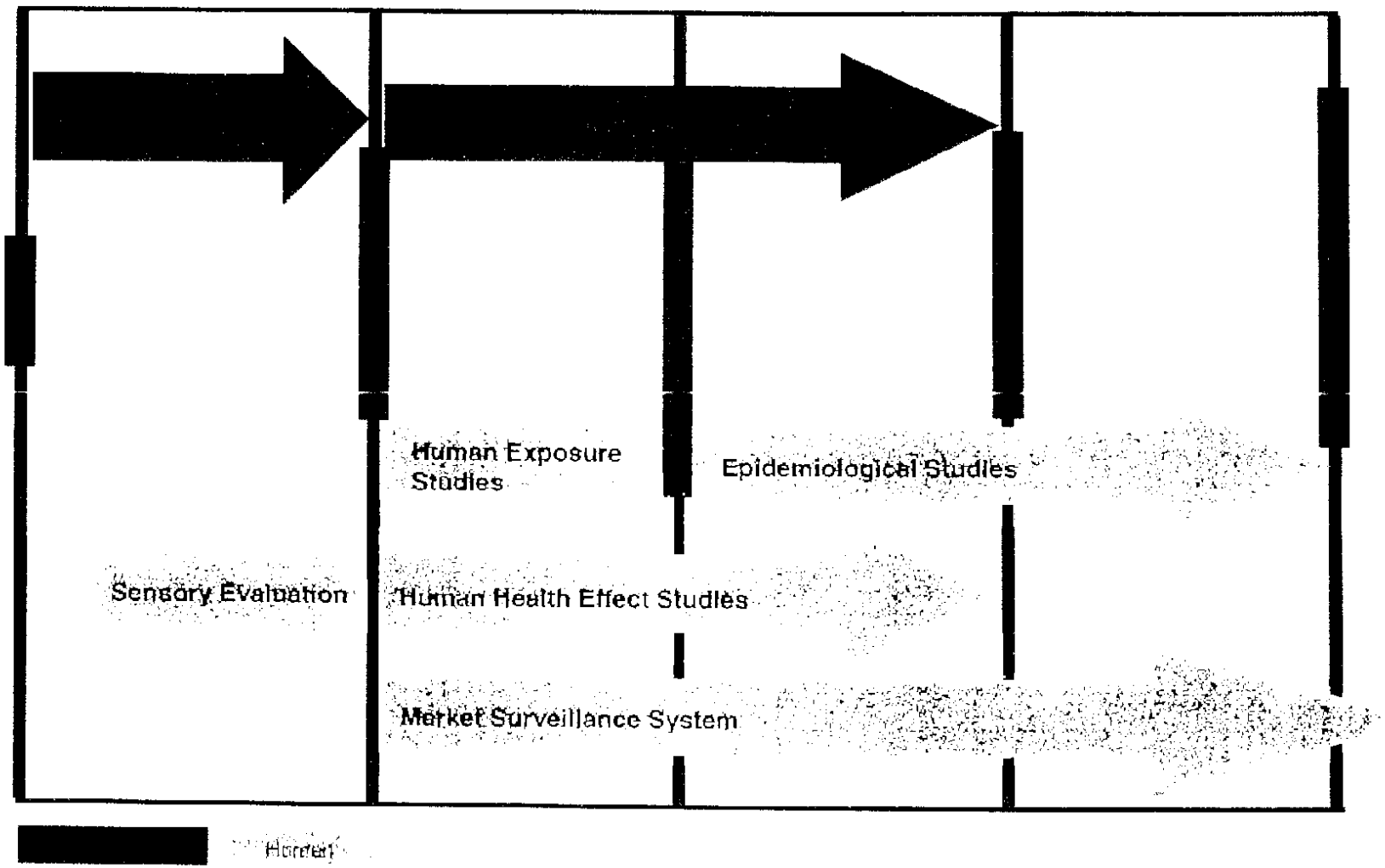
PM3000185965

Basis for PM USA's Comprehensive Approach to Develop and Market Potential Reduced Exposure/Risk Products (PREPS)

- Informed by / modeled upon recognized guidelines, e.g.,
  - Institute of Medicine (Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction, 2001)
- Quality assurance and validation
- Sound scientific judgment
- Ongoing dialogue with the public health and scientific communities

PM3000185966

A Sound and Relevant Harm Reduction Evaluation Process



PM300018596?

Potential Reduced Exposure Products (PREPS) Evaluation

- **Non-clinical (non-human)**
  - Toxicological acceptability testing & toxicological review of ingredients
  - Detection of important toxic properties of chemicals
- **Sensory (human)**
  - Subjective sensory evaluation (e.g., adult smoker liking)
- **Clinical (human)**
  - Evidence of human exposure and potential links to specific health end-points
- **Validation of adult smoker communications**
  - Assessment of potential future communications that would be nonmisleading
- **Surveillance (human)**
  - Impact of new products that would be marketed with claims on smoking behavior (e.g., initiation, exposure, unexpected consequences) as it relates to health
- **Weight of evidence assessment**
  - Conclusions from the combined strength and coherence of inferences appropriately drawn from all of the available evidence
- **External scientific communication**
  - Review of our scientific data, methods and interpretations

Other Guidance from Recognized Sources (Examples)

Animal inhalation toxicity	• American Association for Laboratory Animal Science (AALAS) • Organization for Economic Cooperation and Development (OECD) • International Agency for Research on Cancer (IARC), World Health Organization • US National Toxicology Program (NTP)
Bioanalytical method validation	• US Food and Drug Administration (FDA)
Biological validation of biomarkers	• International Programme on Chemical Safety (IPCS), World Health Organization
Ethical principles to guide human research	• World Medical Association Declaration of Helsinki
Good Clinical Practice	• International Congress on Harmonization (ICH) • US Food and Drug Administration (FDA)

PM3000185969

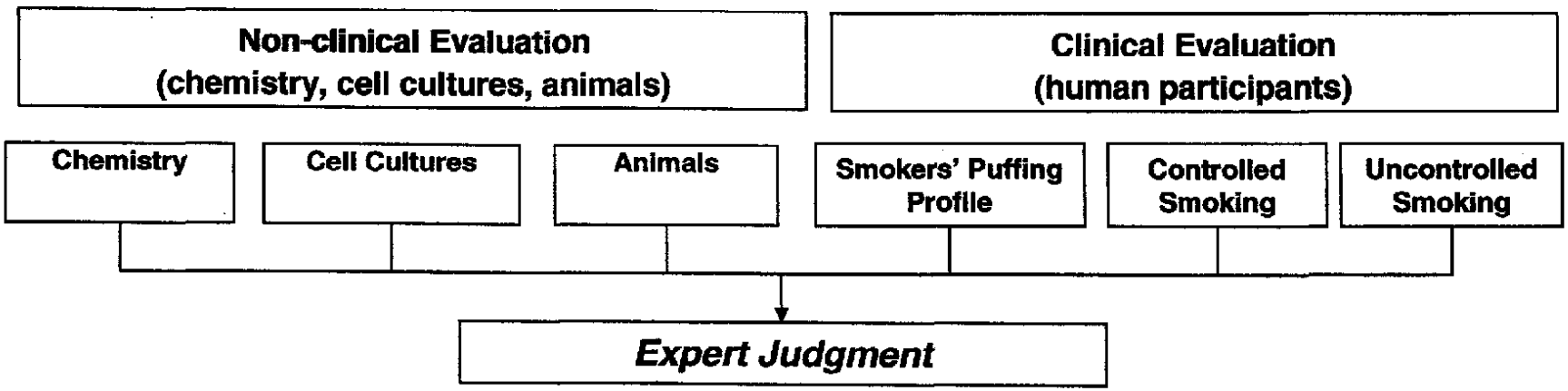
Other Guidance from Recognized Sources (Examples)

Testing method for cell damage	• European data bank of toxicological techniques (INVITTOX)
Toxicological assessment principles	• US Food and Drug Administration (FDA)
Weight of evidence assessment	• International Agency for Research on Cancer (IARC), World Health Organization • US Environmental Protection Agency (EPA) • US Institute of Medicine (IOM) • US National Research Council (NRC) • US National Toxicology Program (NTP) • World Health Organization (WHO)

PM3000185970

Weight of Evidence Assessment

- Conclusions from the combined strength and coherence of inferences appropriately drawn from all of the available evidence
- Addresses IOM Regulatory Principle 4



•What is actually reduced?

–Smoke constituents

–Biological Impact

•How much?

•Relevant to disease?

PM3000185971

Surveillance (human)

- **Objective**

  To monitor the impact of a potential reduced exposure claim on smoking behavior, e.g., initiation, exposure and unexpected consequences as it relates to health.

- **Market Surveillance System**

  Smoking behavior is complex:

  - **Smoking initiation**
  - **Quit attempts**
  - **Maintained abstinence after smoking cessation**
  - **Personal consumption patterns**

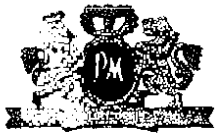
- **Exposure**

- **Unexpected Consequences: Tracking of health-related complaints**

- **Addresses IOM Regulatory Principle 6**

PM3000185972

Responsible Communication



Communication of the quality and quantity of changes to our products will require different communications to the scientific community and consumers.

PM3000185973

Responsible PREP Consumer Communication

- Certain technologies are immediately apparent to the consumer (e.g., Electrically Heated Cigarette Smoking System)

- Taste compromise, or ritual change, may discourage smokers from switching in the absence of a PREP consumer communication.

- Ways to address the concern that communication of reduced exposure attributes to consumers may have an adverse effect on public health:
  - Not make a consumer PREP communication until we can scientifically substantiate reduced exposure
  - Discontinue communication if testing does not continue to support it
  - Evaluate the effect of such communication on overall health impact of smoking

- Evaluate consumer PREP communication of reduced exposure to determine whether adult smokers
  - Receive and understand the entire message including disclaimers, e.g., "not safer"
  - Receive communication that does not encourage unintended and erroneous implicit claims, e.g., "safer", "healthier"

PM3000185974

Summary:

Comprehensive Process to Assess Exposure Reduction

- The scientific substantiation of reduced exposure from cigarette products requires a comprehensive process that takes the data contributed by a battery of relevant and validated test methods into consideration.

- In the absence of comprehensive regulation, PM USA is developing and using such a process and continues to gather data.

PM3000185975

Exposure and its Measurement

- Actual exposure to smokers is an integral part of cigarette harm reduction evaluation

- PM USA will incorporate such data in its harm reduction evaluation

PM3000185976

Assessment of Exposure

- Requires adult smokers to participate

- Types of investigations
  - Population studies – current market
  - Clinical switching studies – PREPs*

- Tools
  - Questionnaires (e.g., daily cigarette consumption)
  - Smoke constituent yields (modeling)
  - Human smoking topography (puffing profiles)
  - Biomarkers of exposure

* PREPs – potential reduced exposure/risk products

PM3000185977

Exposure is Measured Only in Part by Human Topography

- Human topography:
  Set of parameters exhibited by humans during the smoking process.

- Two distinct phases:
  - **Puffing:** closure of soft palate which limits smoke access to the mouth only
  - **Inhalation/exhalation:** smoke mixing with a dilution volume, transport to lungs

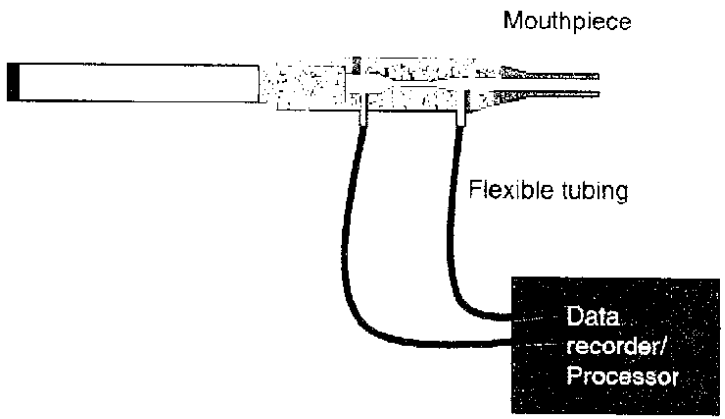
Smoking Topography	*Post Topography Processes*	*Metabolism*
• puff duration • puff volume • puff frequency • puff interval	• depth of inhalation • retention time • % puff inhaled/mouth leak • dilution volume • deposition	• age • gender • genetic polymorphisms • enzyme induction • body composition • physical fitness

PM3000185978

Exposure: Human Smoking Topography

PM USA has conducted research into puffing profiles of adult smokers.

CReSSmicro™ device[1]



Puffing Parameters

- Puff Volume
- Puff Duration
- Inter-Puff Interval
- Peak Flow
- Time of Peak Flow
- Puffs per Cigarette
- Time to First Puff
- Time to Removal
- Date and Time

PM3000185979

[1] **Clinical Research Support System (CReSS) manufactured by Plowshare Technologies, Inc., MD**

Instrument Validation Issues

- Accuracy and precision of measurements
  - Varies with puff profile
  - Threshold adjustments
  - Relative vs. absolute values
- Temporal variation
- Resulting in, e.g.:
  - Puff duration underestimated, esp. at low flows
  - Missed puffs
  - Non-plausible puff volumes

PM3000185980

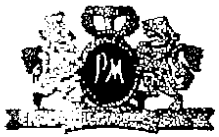
Validated Biomarkers of Exposure

BIOMARKER	BIOFLUID	SMOKE CONSTITUENT	SMOKE PHASE[b]
Carboxyhemoglobin	Blood	Carbon monoxide	GVP
Cotinine	Blood	Nicotine	PP
Nicotine and nicotine metabolites[a]	Urine	Nicotine	PP
NNAL and NNAL-glucuronide	**Urine**	**NNK**	**PP**
Hb adducts of 3- and 4-aminobiphenyl	Blood	3- and 4-aminobiphenyl	PP
1-Hydroxypyrene, glucuronide, sulfate	Urine	Pyrenes (PAHs)	PP
3-Hydroxypropylmercapturic acid (3-HPMA)	Urine	Acrolein	GVP
Monohydroxy-3-butenyl mercapturic acid (MHBMA)	Urine	1,3-butadiene	GVP
S-Phenylmercapturic acid	Urine	Benzene	GVP

[a] cotinine, 3-hydroxycotinine, nicotine-*N*-glucuronide, cotinine-*N*-glucuronide, and *trans*-3'-hydroxycotinine *O*-glucuronide;
[b] GVP: gas-vapor phase; PP: particulate phase;
[c] 24-h urine collection

PM3000185981

Exposure: Population Studies



- Measurements of actual human exposure.
- Limited baseline data exist for population exposure to cigarette smoke.
- Current machine-derived and topography data insufficient for full evaluation of actual human exposure.
- Use of biomarkers of exposure.
- *Total Exposure Study*

PM3000185982

Total Exposure Study (TES)

A statistically powerful cross-sectional observational study

to determine the exposure of adult US cigarette smokers to cigarette smoke:

- To compare selected biomarkers among adult US smokers and non-smokers
- Covering all tar yield categories

PM3000185983

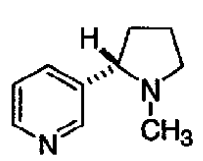
TES - Study Design and Population

- Ambulatory, multi-center study with approx. **4,500** participants in 5 parallel groups
  - Approx. **3,500** adult smokers in 4 groups based on FTC tar delivery categories, representative of adult US smokers population regarding:
    - age
    - gender
    - geographic location
    - ethnic distribution
    - socioeconomic distribution (income and education)
  - Approx. **1000** adult non-smokers
- **41** Sites across US

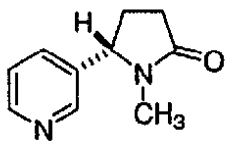
PM3000185984

Nicotine and Metabolites in 24-h Urine

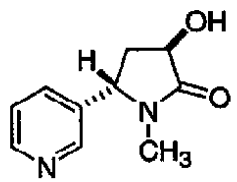
Molar sum = Nicotine equivalents (96% nicotine uptake)*



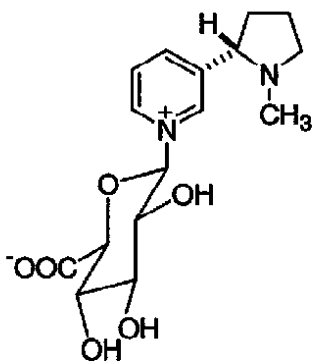
Nicotine (9%)



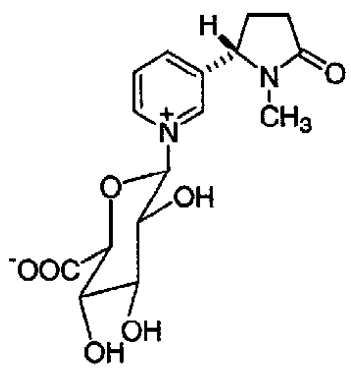
Cotinine (9%)



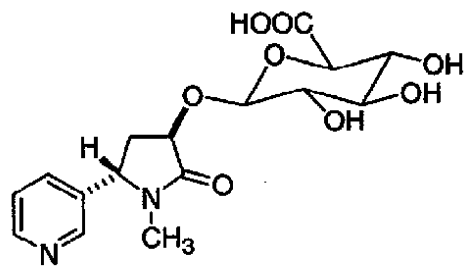
trans-3'-hydroxycotinine (36%)



Nicotine-*N*-Glucuronide (5%)



Cotinine-*N*-Glucuronide (14%)

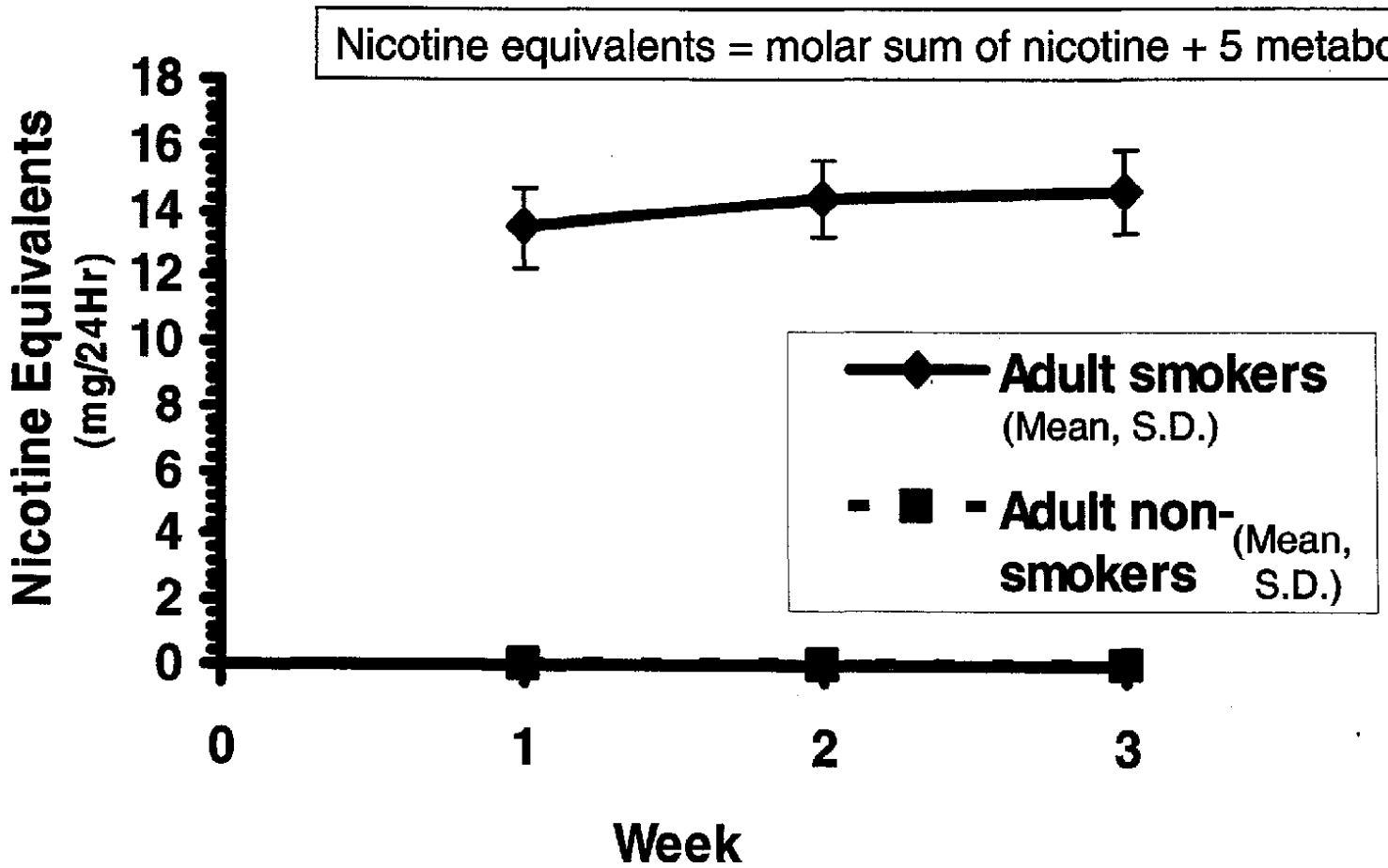


trans-3'-Hydroxycotinine-*O*-Glucuronide (23%)

* Andersson et al. (1997)

PM3000185985

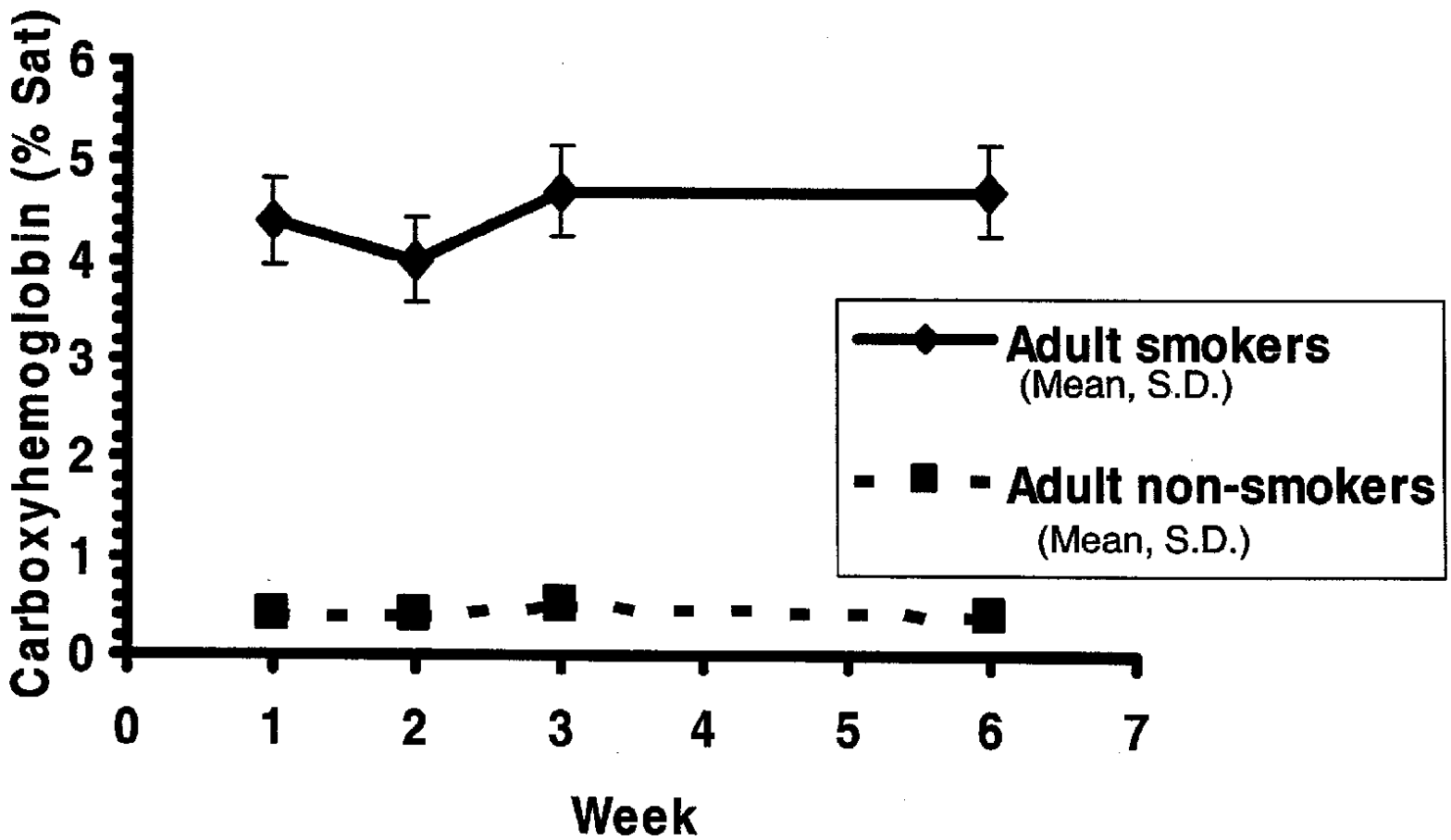
Pilot TES – Nicotine Equivalents



Data (mean ± SD); 72 adult smokers (3.0-6.9 mg FTC tar/cig.), 68 adult nonsmokers
Kinser et al. (2002), 8th annual meeting of SRNT, Savanah, GA (in part)

PM3000185986

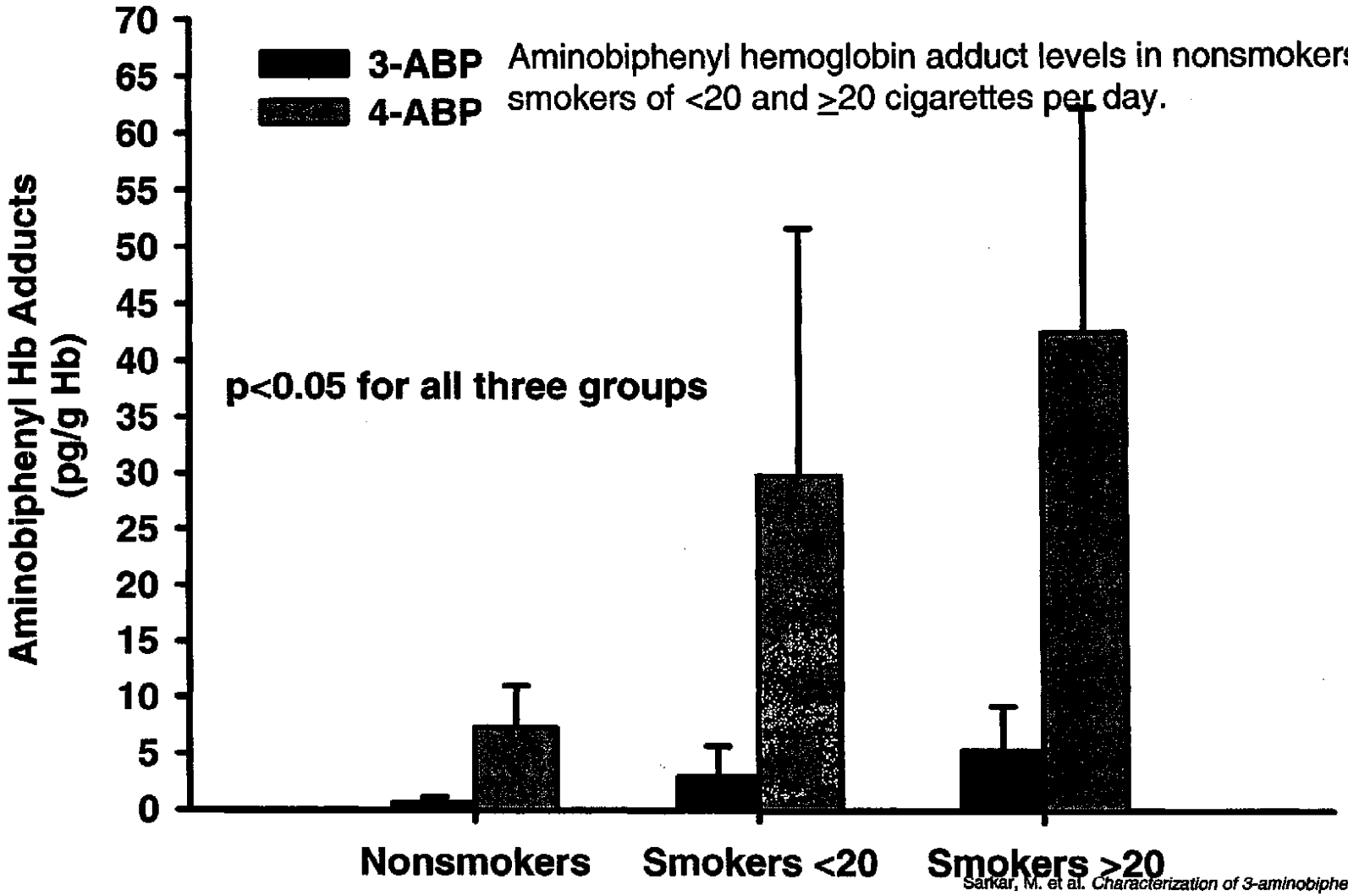
Pilot TES - Carboxyhemoglobin



Not yet published

PM3000185987

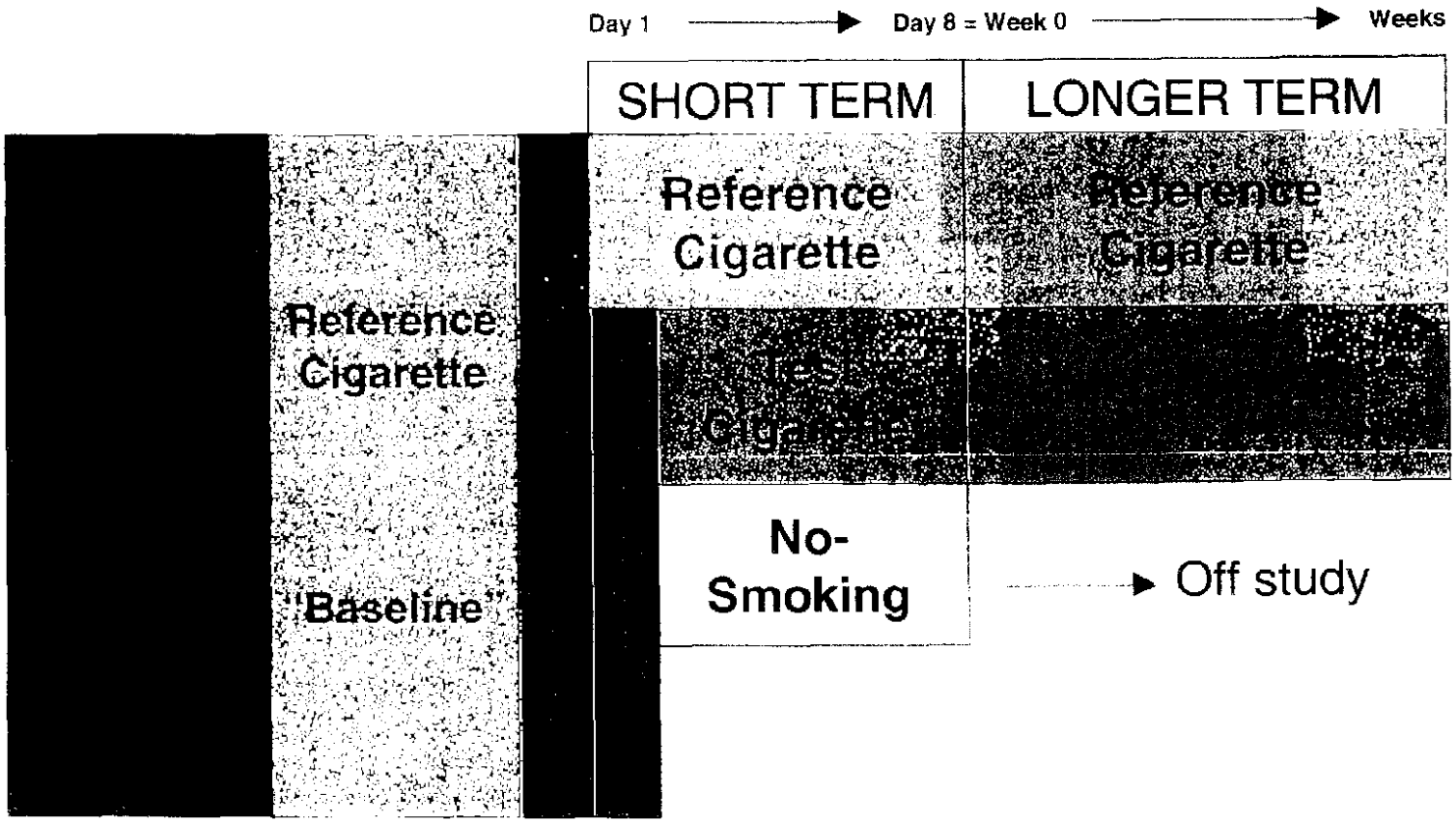
Pilot TES – Aminobiphenyl Hb Adducts



Sarkar, M. et al. *Characterization of 3-aminobiphenyl and 4-aminobiphenyl hemoglobin adducts in adult smokers and non-smokers phenotyped for CYP 1A2 and NAT2 activity.* Poster presented at the 94th Annual Meeting of American Association for Cancer Research, Washington, D.C., July 11-14, 2003.

PM300018598B

Exposure: Clinical Evaluation Methodology

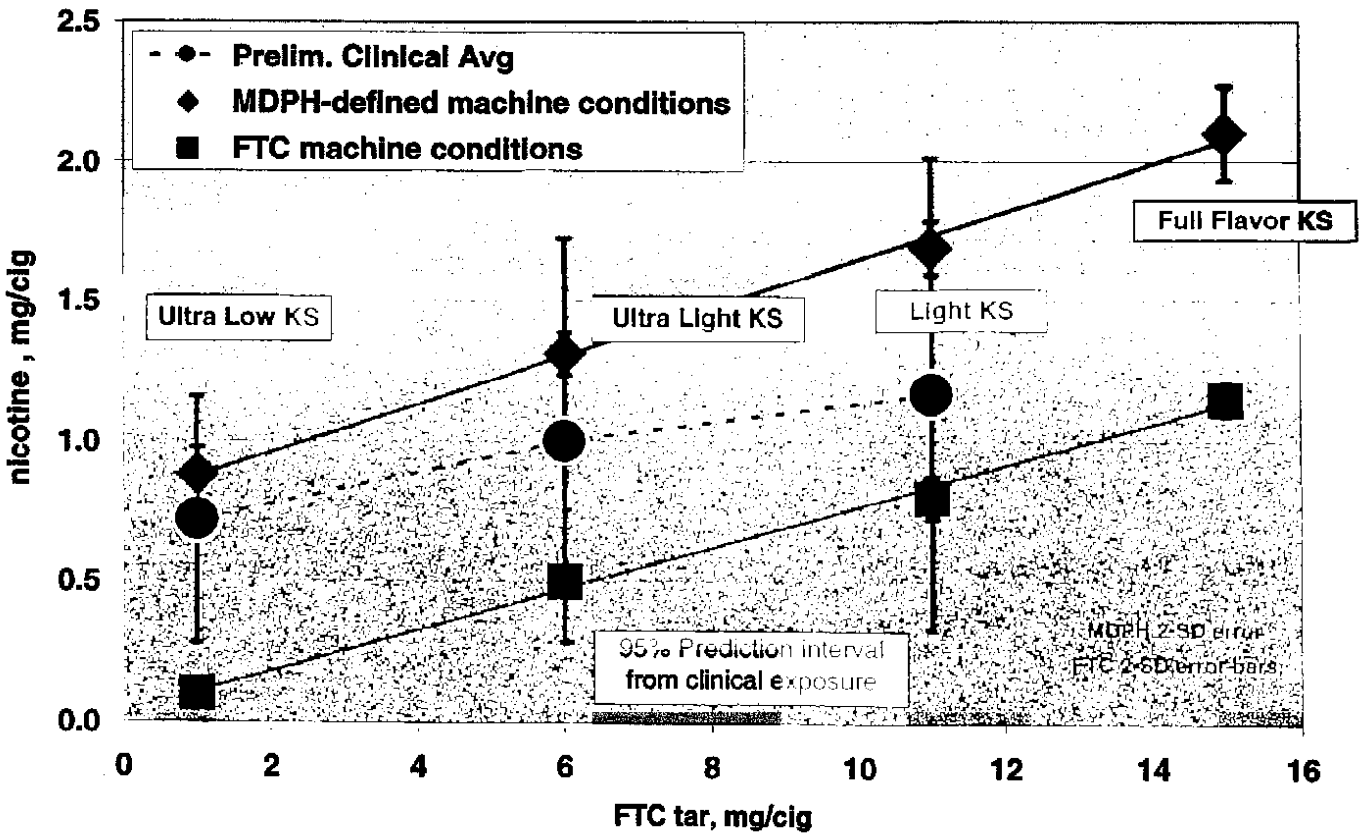


- **Collection of clinical exposure data from adult smokers under defined conditions**
- **Randomized clinical studies with forced switching**
- Usually 20 adult smokers per group
- Controlled or uncontrolled smoking
- Biomarkers assessed at baseline and at various times after switching

PM3000185989

Comparison of Human Exposure and Machine-derived Smoke Constituent Yields

Preliminary clinical switching studies nicotine exposure results relative to machine yields from Massachusetts Dept. of Health and FTC defined conditions



PM3000185990

Summary

- We are making progress in reducing levels of TSNAs in the domestic tobacco we purchase for our cigarette products, but have not yet seen a reduction in smoke of conventional lit-end cigarettes.
- Promising technologies are being developed to reduce harmful compounds in the gas/vapor phase (SCoR program).
- We have reduced TSNAs and PAHs in cigarette smoke by heating rather than burning tobacco (Electrically Heated Cigarette Smoking System).
- Human exposure can best be assessed using validated biomarkers.
- Smoke constituent yields and human topography can contribute to our understanding of exposure when validated/standardized methods are available and variability, such as those originating from the tobaccos, are taken into consideration.
- The scientific substantiation of reduced exposure from cigarette products requires a comprehensive process that takes the data contributed by a battery of relevant and validated tests into consideration.

PM USA Current Plans re PREPs

- Continue to evaluate products utilizing SCoR and EHCSS technology to determine whether they meet the Institute of Medicine (IOM) criteria for substantiation of reduced exposure claims.

- Continue to evaluate how best to communicate scientifically substantiated reduced exposure claims to adult smokers clearly and in a manner that is not "false or misleading".

- In the interim, test market products utilizing SCoR technology to gauge adult smoker acceptance of taste/flavor without reduced exposure claims (similar to ongoing testing of EHCSS technology).

PM3000185992